REMARKS/ARGUMENTS

Claims 54-69 are currently pending in this application. Claims 54, 57 and 64 have been amended and support can be found in the claims and specification as originally filed.

With respect to all claims, Applicants have not dedicated, disclaimed, or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants reserve the right to pursue prosecution of any presently excluded claim embodiments in future continuation and/or divisional applications.

Double patenting rejections

Applicants request that the Examiner hold these rejections in abeyance until notice of allowable subject matter.

Objections

Claims 57 and 64 have been amended to address the Examiner's objections.

Rejections under 35 U.S.C. §112, second paragraph - Definiteness

Claims 64-69 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 64 has been amended to recite "wherein said first polypeptide and said second polypeptide dimerize to form a bispecific antibody." Applicants submit that as currently amended, claim 64 and all claims depending therefrom are clear and definite. In light of the foregoing, Applicants respectfully request the withdrawal of this rejection.

Rejections under 35 U.S.C. §112, first paragraph – Written description

Claims 64-69 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement. The Examiner asserts that bispecific antibodies "comprising common light chains where the definition of common light chains is one where the sequences are not identical constitutes new matter." (page 6 of the April 10, 2008 Office Action).

Applicants respectfully disagree. The present specification provides that

> [p]anels of antibodies were generated against at least two different antigens by panning a phage display library ... [and t]he light chain sequences were compared with respect to the variable light chain amino acid sequences.
>
> Useful light chains from the compared panels are those having amino acid sequence identity of at least 80%, preferably at least 90%, more preferably at least 95%, and most preferably 100% identity. A common light chain sequence is a sequence designed to be an approximation of the two compared light chain sequences ... [and w]here the compared light chains differ as described above, the common light chain may differ from one or the other, or both, of the compared light chains from the library clones. [emphasis added] (page 22, line 18 to page 23, line 5)

As such, the present invention clearly contemplates common light chains where the amino acid sequence is not identical. The specification further provides that in

> a case in which the common light chain differs from one or the other, or both of the library clones, it is preferred that the differing residues occur outside of the antigen binding CDR residues of the antibody light chain. [emphasis added] (page 23, lines 5-9)

As such, common light chains "identical to each other within the complementarity determining regions (CDRs) and different to each other outside of the CDRs" are fully supported by the instant specification.

In addition, the Examiner asserts that there are "instances in the specification that applicant conceived of methods of making bispecific antibodies where all of the binding domains comprise a light chain having the same sequence" (page 7 of the Office Action). Applicants respectfully submit that this assertion is improper. It is a basic claim construction principle that limitations from the specification may not be imported into the claims (*CollegeNet, Inc. v. ApplyYourself, Inc.*, 418 F.3d 1225, 1231 (Fed Cir. 2005). As such, the Examiner's considerations as to claims 64-69 in this regard are moot.

Based on the foregoing, Applicants respectfully submit that the present specification provides adequate written description for claim 64 and all claims depending therefrom. As such, no new matter has been introduced and the rejection should be withdrawn.

Claim 62 stands rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement. The Examiner asserts that claim 62 "is drawn to a bispecific antibody having a multimerization domain with a protuberance and cavity interaction in addition to a disulfide bond ... [and] an examination of the specification

does not reveal any support for the subject matter of claim 62." (page 8 of the April 10, 2008 Office Action).

Applicants respectfully disagree and submit that the present specification provides adequate support for claim 62. Regarding the promotion of a polypeptide-polypeptide interaction by the multimerization domain, the specification provides that an "[i]nteraction may be promoted at the interface by the formation of protuberance-into-cavity complementary regions; the formation of non-naturally occurring disulfide bonds; ... and hydrophilic regions." [emphasis added] (page 11, lines 23-27). As such, Applicants submit that the present specification supports the embodiment of a protuberance-into-cavity interface and a non-naturally occurring disulfide bond, and therefore request that the rejection be withdrawn.

Rejections under 35 U.S.C. §102

Claims 54 and 56 stand rejected under 35 U.S.C. §102(b) as allegedly being anticipated by *de Kruif*, et al. (1996) J. Biol. Chem. 271(13): 7630-7634, 1996 (hereinafter referred to as "de Kruif-A") as evidenced by *de Kruif*, et al. (1995) J. Mol. Biol. 248: 97-105 (hereinafter referred to as "de Kruif-B"). The Examiner argues that

> de Kruif-A teaches methods for making bispecific antibodies from semi-synthetic antibody phage display libraries, such as the libraries of Hoogenboom and Winter (1992), Nissim(1994) or de Kruif (1995) (see page 7632, 2nd column). de Kruif-B provides evidence that libraries such as that of Hoogenboom and Winter(1992) or Nissim(1994) are libraries with collections of V_H genes combined with one light chain. (page 9 of the April 10, 2008 Office Action)

Applicants respectfully disagree and submit that the Examiner has not set forth a proper anticipation rejection. According to M.P.E.P §2131, a "claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). The Examiner has failed to establish that a single reference either expressly or inherently describes each and every element as set forth in claims 54 and 56. de Kruif-B describes the construction of a "semi-synthetic phage display library of human scFV fragments" in which "semi-synthetic V_H regions were cloned into seven vectors containing light chains encoded by members of the $V_\kappa 1$ to $V_\kappa 4$ and $V_\lambda 1$ to $V_\lambda 3$ gene families." [emphasis added] (page 98, 2nd paragraph of 1st column and 1st paragraph of 2nd column). de Kruif-A discloses the construction of leucine zipper dimerized scFv

antibodies based upon certain clones isolated from the library of de Kruif-B (page 7630, 1st paragraph of 2nd column under "Materials and Methods"). As such, the dimerized scFv antibodies of de Kruif-A were derived from a library constructed from multiple light chains. The Hoogenboom and Winter (1992) and Nissim (1994) libraries mentioned were not the subject of either de Kruif publication. Therefore, de Kruif-A neither expressly or inherently describes each and every element as set forth in claims 54 and 56. As a result, the reference cannot anticipate claims 54 and 56 and the Applicants respectfully request the withdrawal of the rejection.

Rejections under 35 U.S.C. §103

Claims 54, 55, 58-61 and 63 stand rejected under 35 U.S.C. §103(a) as being allegedly unpatentable over *Carter*, et al. WO 96/27011 published September 6, 1996; cited in IDS (hereinafter referred to as "Carter-B") in view of de Kruif-A and further in view of de Kruif-B. The Examiner argues that "Carter-B teaches methods of making bispecific antibodies comprising culturing a host cell comprising a nucleic acid encoding a first polypeptide and nucleic acid encoding at least one additional polypeptide" (page 11 of the April 10, 2008 Office Action) but states that "Carter-B fails to specifically teach that the light chain variable domain for one binding domain formed by the first polypeptide will have the same amino acid as the light chain variable domain for other binding domain formed by the at least one other polypeptide." (*Id.* at page 12). The Examiner further states that

> de Kruif-A teaches methods for making bispecific antibodies from semi-synthetic antibody phage display libraries, such as the libraries of Hoogenboom and Winter (1992), Nissim(1994) or de Kruif (1995) (see page 7632, 2nd column). de Kruif-B teaches that libraries such as that of Hoogenboom and Winter(1992) or Nissim(1994) are libraries with collections of V_H genes combined with one light chain. (*Id.*)

Based on the foregoing, the Examiner asserts that a prima facie case of obviousness has been established. Specifically, the Examiner argues that it would have obvious to one of ordinary skill in the art at the time the invention was made to combine Carter-B with de Kruif-A and de Kruif-B to make the claimed inventions because Carter-B teaches that

> bispecific antibodies may be made using methods of forming interfaces to promote heterodimerization of two different polypeptides, ... [and] nucleic acids encoding such polypeptides may be derived from known phage libraries (*Id.*)

In addition, the Examiner asserts that because

> de Kruif-A and de Kruif-B show that antibody phage libraries containing multiple heavy chains paired with the same light chain were known in the art and useful for isolating scFv fragments that bound to different antigens, it is clear that the prior art provided antibody phage libraries that encode binding domains that are the same as those of the claimed bispecific antibodies where the sequence of the light chain is the same for each binding domain. (*Id.*)

Finally, the Examiner argues that

> it would have been obvious to try to use the methods of Carter-B, which suggested the use of phage libraries as a source of nucleic acid sequences to encode the binding domains of the first and second polypeptides, with the phage libraries taught by de Kruif-A and de Kruif-B, especially since de Kruif-A suggests that bispecific antibodies may be made from such antibody phage libraries. [emphasis added] (*Id.* at pages 12-13)

Applicants respectfully disagree and submit that the Examiner has failed to establish a prima facie case of obviousness. An obviousness inquiry is controlled by the factors articulated by the Supreme Court in *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1 (1966), including: 1) the scope and content of the prior art; 2) the differences between the prior art and the claims; 3) the level of ordinary skill in the pertinent art; and 4) objective evidence of nonobviousness. In addition, a long line of Federal Circuit decisions has established that a patent claim is only proved obvious if the prior art, the problem's nature, or the knowledge of a person of ordinary skill in the art provides some motivation or suggestion to combine the prior art teachings (the "teaching, suggestion, or motivation" or "TSM" test). While the Supreme Court has recently rejected a rigid application of the TSM test, it stated that the Graham Deere factors still control an obviousness inquiry. See *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727 (2007). Moreover, the Court indicated that there is "no necessary inconsistency between the idea underlying the TSM test and the Graham analysis." KSR, 127 S. Ct at 1731. The Court specifically acknowledged the importance of identifying "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does" in an obviousness determination. *Id.* As long as the test is not applied as a "rigid and mandatory" formula, that test can provide "helpful insight" to an obviousness inquiry. *Id.*

Applying these principles, Applicants will show that the Examiner has not established a *prima facie* case of obviousness because **(A)** the references cited do not teach or suggest all limitations of the currently pending claims, **(B)** the Examiner has failed to articulate all the elements required for an "obvious to try" rationale, thereby failing to identify a reason that

would have prompted a person of ordinary skill in the art to combine the elements in the way the Applicants' presently claimed invention does, **(C)** the references teach away from the present invention, and **(D)** the Examiner has based obviousness on improper hindsight.

A. The references do not teach or suggest all the elements

As previously argued above, the scFv fragments modified in de Kruif-A to include a Fos or Jun leucine zipper were originally derived from a phage antibody library of de Kruif-B, which contained several different light chains and not a single light chain. As such, the references cited by the Examiner fail to teach or suggest each and every element of claims 54 and 59.

B. Failure to articulate an "obvious to try" rationale

In *KSR International v. Teleflex, Inc.*, the U.S. Supreme Court considered the "obvious to try" rationale and concluded that

> [w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. [emphasis added] (127 S. Ct. at 1742).

According to the Examination Guidelines for Determining Obviousness Under 35 U.S.C. §103 in View of the Supreme Court Decision in *KSR International v. Teleflex, Inc.* (hereinafter "KSR Guidelines"), in order to reject a claim based upon an "obvious to try" rationale, the Examiner must articulate the following.

> (1) a finding that at the time of the invention, there had been a recognized problem or need in the art, which may include a design need or market pressure to solve a problem;
>
> (2) a finding that there had been a finite number of identified, predictable potential solutions to the recognized need or problem;
>
> (3) a finding that one of ordinary skill in the art could have pursued the known potential solutions with a reasonable expectation of success; and
>
> (4) whatever additional findings based on the *Graham* factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness. (p. 57532 of the Federal Register, Vol. 72, No. 195, October 10, 2007)

Applicants respectfully submit that the Examiner has not articulated elements (1) to (4) above. Clearly, the Examiner's burden for establishing an "obvious to try" rationale has been set forth by the *KSR* Court and the KSR Guidelines. As the Examiner has failed to meet this burden, a conclusion that Applicants' claims are obvious cannot be reached.

Furthermore, as discussed above, the *KSR* Court specifically acknowledged the importance of identifying "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does" in an obviousness determination. KSR, 127 S. Ct at 1731. Applicants submit that quite the opposite is true. In view of de Kruif-A and de Kruif-B, a person of ordinary skill in the art, in fact, would have no good reason to make the combination asserted by the Examiner because according to de Kruif-A and de Kruif-B the construction of phage antibody libraries strongly favors large size and diversity achievable through the use of multiple light chains such as those disclosed in de Kruif-B. For example, de Kruif-B provides that a

> major goal of recombinant antibody technology is to develop Phab libraries of large size and diversity to facilitate the isolation of antibodies of every conceivable specificity, among them antibodies with high affinity. A major determinant of diversity is the source of antibody genes used as building blocks to construct the library. (page 97, 1st paragraph of 2nd column)

In fact, the authors of de Kruif-B demonstrate a commitment to achieving a library of large size and diversity by selecting seven different light chains (page 98, 2nd paragraph of 1st column and 1st paragraph of 2nd column). Increased library size and diversity are considered major goals by de Kruif-B. Therefore, in view of de Kruif-B, a person of ordinary skill in the art would seek to construct a library having as many diverse components as possible, including multiple light chains. As a result, in view of the teachings of de Kruif-B, there is no good reason for a person of ordinary skill in the art to decrease the number of light chains, let alone use a single light chain, when constructing an phage antibody library.

C. References teach away from the present invention

As the Examiner is aware, a "prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984)" (M.P.E.P. §2141.02 VI). Applicants respectfully submit that de Kruif-A and de Kruif-B teach away from the present invention. As the cited references teach,

the construction of phage antibody libraries strongly favors large size and diversity and such large size and diversity would be achievable through the use of multiple light chains such as those disclosed in de Kruif-B. Thus, de Kruif-A and de Kruif-B teach away from a common light chain. Accordingly, Applicants submit that neither reference can form the basis of an obviousness rejection.

D. Improper hindsight

The *KSR* Court specifically acknowledged that a "fact-finder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning." 127 S. Ct at 1742 (citing *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 36 (1966)). Applicants respectfully submit that the Examiner's conclusion of obviousness is based upon improper hindsight reasoning. As discussed above, the references cited by the Examiner fail to teach or suggest each and every element of the Applicants' currently pending claims. Indeed, there is no doubt that the Examiner has used the disclosure of the present application to pick and choose selected portions of Carter-B, which were then combined with de Kruif-A and de Kruif-B in an attempt to recreate the claimed invention. Applicants respectfully submit that the Examiner's conclusion is based upon an improper hindsight reconstruction of the claimed invention, which, instead of looking at the prior art as a whole, picks and chooses teachings that appears to support a finding of obviousness, while completely disregarding others.

Claims 54, 56, 57-60 and 63 stand rejected under 35 U.S.C. §103(a) as being allegedly unpatentable over Hu et al. (1996) Cancer Research, 56:3053-3061; cited in IDS (hereinafter referred to as "Hu") in view of de Kruif-A and further in view of de Kruif-B. The Examiner argues that "Hu teaches that scFv dimers ... [but] fails to teach that the two scFv bind to different antigens (bispecificity) ... [and a]lthough the light chains of Hu's scFv domains are the same for each scFv domain this is because the two scFv domains bind to the same antigen." (page 13 of the April 10, 2008 Office Action). The Examiner relies upon de Kruif-A and de Kruif-B for the same reasons as discussed previously for the rejection based upon Carter-B. Based on the foregoing, the Examiner asserts that a prima facie case of obviousness has been established. Specifically, the Examiner argues that it would have obvious to one of ordinary skill in the art at the time the invention was made to combine Hu with de Kruif-A and de Kruif-B to make the claimed inventions because Hu teaches that

> scFv dimers may be made using methods of forming interfaces to promote heterodimerization of two different polypeptides (*Id.* at page 14)

In addition, the Examiner asserts that because

> de Kruif-A and de Kruif-B show that antibody phage libraries containing multiple heavy chains paired with the same light chain were known in the art and useful for isolating scFv fragments that bound to different antigens and that scFv libraries are useful for finding scFv domains for a bispecific antibody, it is clear that the prior art provided antibody phage libraries that encode binding domains that are the same as those of the claimed bispecific antibodies where the sequence of the light chain is the same for each binding domain. (*Id.*)

Finally, the Examiner argues that

> it would have been obvious to try to combine the methods of Hu, which teaches a method for making an scFv dimer, with the methods of using phage libraries as taught by de Kruif-A and de Kruif-B, to make bispecific scFv dimers as suggested by de Kruif-A. [emphasis added] (*Id.*)

Applicants respectfully disagree and submit that the Examiner has failed to establish a prima facie case of obviousness.

Applicants respectfully disagree and submit that the Examiner has not established a *prima facie* case of obviousness because **(A)** the references cited do not teach or suggest all elements of the currently pending claims, **(B)** the Examiner has failed to articulate all the elements required for an "obvious to try" rationale, thereby failing to identify a reason that would have prompted a person of ordinary skill in the art to combine the elements in the way the Applicants' presently claimed invention does, **(C)** the references teach away from the present invention, and **(D)** the Examiner has based obviousness on improper hindsight.

A. The references do not teach or suggest all the elements

As previously argued above, the scFv fragments modified in de Kruif-A to include a Fos or Jun leucine zipper were originally derived from a phage antibody library of de Kruif-B, which contained several different light chains and not a single light chain. As such, the references cited by the Examiner fail to teach or suggest each and every element of claims 56, 67, 73, and any claims depending therefrom.

B. Failure to articulate an "obvious to try" rationale

Applicants respectfully submit that the Examiner has not articulated elements (1) to (4) above as set forth in the KSR Guidelines discussed above. As the Examiner has failed to meet this burden, a conclusion that Applicants' claims are obvious cannot be reached.

Furthermore, as discussed above, the *KSR* Court specifically acknowledged the importance of identifying "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does" in an obviousness determination. KSR, 127 S. Ct at 1731. Applicants submit that quite the opposite is true. A person of ordinary skill in the art, in fact, would have no good reason to make the combination asserted by the Examiner because the minibodies of Hu were constructed by dimerizing the T84.66.212 scFv using CH3 domains (page 3056 1st column under "Design of Minibodies"). The protocols described by Hu involve the selection of a distinct scFv having one heavy chain and one light chain as a template minibody construction. If the Examiner's asserted combination were to be followed, two distinct scFv molecules, each specific for a different antigen, would have to be selected from a library such as the one described in de Kruif-B. However, as discussed above, the library of de Kruif-A was constructed using seven different light chains so the light chain for each of the two distinct scFv molecules would not be the same. Given the stated goals of large size and diversity in a phage antibody library, discussed above and below, there is no good reason to reduce the number of light chains from seven to one in the de Kruif-B library in an attempt to identify suitable scFv molecules for use with the protocols of Hu.

In addition, as discussed above, de Kruif-A and de Kruif-B also provide evidence of the lack of a good reason to make the combination asserted by the Examiner because the construction of phage antibody libraries strongly favors large size and diversity that might be achieved through the use of multiple light chains such as those disclosed in de Kruif-B. For example, de Kruif-B provides that a

> major goal of recombinant antibody technology is to develop Phab libraries of large size and diversity to facilitate the isolation of antibodies of every conceivable specificity, among them antibodies with high affinity. A major determinant of diversity is the source of antibody genes used as building blocks to construct the library. (page 97, 1st paragraph of 2nd column)

In fact, the authors of de Kruif-B demonstrate a commitment to achieving a library of large size and diversity by selecting seven different light chains (page 98, 2nd paragraph of 1st

column and 1st paragraph of 2nd column). Increased library size and diversity are considered major goals of de Kruif-B. Consequently, in view of de Kruif-B, a person of ordinary skill in the art would seek to construct a library having as many diverse components as possible, including multiple light chains. Therefore, in view of de Kruif-A and de Kruif-B, there is no good reason for a person of ordinary skill in the art to decrease the number of light chains, let alone use a single light chain, when constructing an phage antibody library.

C. References teach away from the present invention

As the Examiner is aware, a "prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984)" (M.P.E.P. §2141.02 VI). Applicants respectfully submit that de Kruif-A and de Kruif-B teach away from the present invention. As the cited references teach, the construction of phage antibody libraries strongly favors large size and diversity and such large size and diversity would be achievable through the use of multiple light chains such as those disclosed in de Kruif-B. Thus, de Kruif-A and de Kruif-B teach away from a common light chain. Accordingly, Applicants submit that neither reference can form the basis of an obviousness rejection.

D. Improper hindsight

The *KSR* Court specifically acknowledged that a "fact-finder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning." 127 S. Ct at 1742 (citing *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 36 (1966)). Applicants respectfully submit that the Examiner's conclusion of obviousness is based upon improper hindsight reasoning. As discussed above, the references cited by the Examiner fail to teach or suggest each and every element of the Applicants' currently pending claims. Indeed, there is no doubt that the Examiner has used the disclosure of the present application to pick and choose selected portions of Hu, which were then combined with de Kruif-A and de Kruif-B in an attempt to recreate the claimed invention. Applicants respectfully submit that the Examiner's conclusion is based upon an improper hindsight reconstruction of the claimed invention, which, instead of looking at the prior art as a whole, picks and chooses teachings that appears to support a finding of obviousness, while completely disregarding others.

CONCLUSION

In light of the above amendments, Applicants believe that this application is now in condition for immediate allowance and respectfully request that the case be passed to issue.

Please charge any fees that might become applicable, including any fees for extension of time, or credit overpayment to Deposit Account No. 07-1700, referencing Attorney's Docket No. GNE-0215R2C1.

Respectfully submitted,
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Dated: August 10, 2008

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